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APPEAL BRIEF

Attorney Docket No. 31580-702.201

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re the Application of: Applicants: Defu Zeng Serial No.: 09/844,544 Filed: April 27, 2001 Title: Methods for inhibition of polyclonal B cell activation and immunoglobulin class switching to pathogenic autoantibodies by blocking CD1-mediated interactions	Confirmation No.: 3043 Group Art Unit: 1644 Examiner: Marianne NMN Dibrino Customer No. 021971

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APPELLANTS' BRIEF PURSUANT TO 37 C.F.R. § 41.37

Appellants submit this brief in accordance with the provisions of 37 C.F.R. § 41.37 in response to the Non-Final Rejection mailed February 6, 2008. Under the provisions of 37 C.F.R. §41.31, submission of this appeal is proper, as the pending claims have been twice rejected. Appellants' Notice of Appeal was filed May 2, 2008.

The fee for filing a Brief in Support of an Appeal under 37 C.F.R. §41.20(b)(2) is electronically submitted herewith. A Petition for Extension of Time is requested for a reply within the fifth month and the fee set forth under 37 C.F.R. §1.17(a)(1) are electronically submitted herewith. This Appeal Brief is therefore timely filed.

I. REAL PARTY IN INTEREST

The real party in interest is The Board of Trustees of the Leland Stanford Junior University (Assignee) by virtue of an assignment executed by the inventors (Appellants) to The Board of Trustees of the Leland Stanford Junior University recorded by the Assignment Branch of the U.S. Patent and Trademark Office on April 27, 2001 at Reel 011771 and Frame 0601.

II. RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any related appeals or interferences.

III. STATUS OF CLAIMS

The application under appeal currently includes claims 15-26. The claims have been twice rejected. Claims 22 stands rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement.

Claims 15-20 and 23-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Amano et al. J. Immunol. 1998, 161: 1710-17 ("Amano"), in view of Kotzin, Cell, 1996; 85: 303-306 ("Kotzin"), Zeng et al., J. Exp. Med. 1998, 187:525-36 ("Zeng"), Blumberg et al., Immunol. Rev. 1995, 147:5-29 ("Blumberg) and Hughes, Drug Discov. Today, 1998; 3(10):439-42 ("Hughes").

Claims 21 and 22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Amano in view of Kotzin, Zeng, Blumberg, Hughes and Merck Manual, 1992, 16th Edition, pages 1317-21 ("Merck Manual").

Claims 15-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Amano in view of Kotzin, Zeng, U.S. Patent No. 6,531,453 (the '453 patent), Blumberg and Hughes.

Claims 15-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Amano in view of Kotzin, Zeng, the '453 patent, Blumberg, Hughes and the Merck Manual.

Claims 15-26 are appealed.

IV. STATUS OF AMENDMENTS

Appellants have submitted no amendments after the final rejection. All amendments prior to filing the notice of appeal have been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent Claim 15 recites a method of treating systemic lupus erythematosus in a human patient comprising administering an effective dose of a CD1d blocking antibody. The preceding method of treatment is described in the specification at least on page 18, paragraph 0066 to page 28, paragraph 0092.

Independent claim 23 recites a method of treating systemic lupus erythematosus in a human patient comprising administering to said patient an effective dose of a CD1d blocking antibody and wherein the effective dose is sufficient to inhibit a pathological polyclonal B cell activation or class switching. The preceding method is described in the specification at least on page 3, paragraph 0012, page 6, paragraphs 0021-0022, page 10, paragraph 0037, page 16, paragraph 0059, and page 26, paragraph 0088.

Independent claim 24 recites a method of treating systemic lupus erythematosus in a human patient comprising administering to said patient an effective dose of a CD1d blocking antibody, wherein the effective dose is sufficient to reduce proteinuria. The preceding method is described in the specification at least on page 4, paragraphs 0014-0015, page 18, paragraph 0066, and page 21 onward, at paragraphs 0075-0076, 0078-0090.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellants respectfully request the Board of Patent Appeals and Interferences to review the following grounds of rejection on appeal:

1. Whether claim 22 complies with the written description requirement under 35 U.S.C. 112, first paragraph.
2. Whether claims 15-20 and 23-26 are patentable under 35 U.S.C. 103(a) over Amano et al. J. Immunol. 1998, 161: 1710-17 ("Amano"), in view of Kotzin, Cell, 1996; 85: 303-306 ("Kotzin"), Zeng et al., J. Exp. Med. 1998, 187:525-36 ("Zeng"), Blumberg et al., Immunol.

Rev. 1995, 147:5-29 ("Blumberg) and Hughes, Drug Discov. Today, 1998; 3(10):439-42 ("Hughes").

3. Whether claims 21 and 22 are patentable under 35 U.S.C. 103(a) over Amano in view of Kotzin, Zeng, Blumberg, Hughes and Merck Manual, 1992, 16th Edition, pages 1317-21 ("Merck Manual").

4. Whether claims 15-26 are patentable under 35 U.S.C. 103(a) Amano in view of Kotzin, Zeng, U.S. Patent No. 6,531,453 (the '453 patent), Blumberg and Hughes.

5. Whether claims 15-26 are patentable under 35 U.S.C. 103(a) Amano in view of Kotzin, Zeng, the '453 patent, Blumberg, Hughes and the Merck Manual.

VII. APPELANTS' ARGUMENTS

Appellants respectfully submit that the specification provides sufficient written description for claim 22. In addition, Applicants respectfully submit that claims 15-22 are in proper form and are patentable over the prior art of record.

A. THE EXAMINER ERRED IN REJECTING CLAIM 22 AS FAILING TO COMPLY WITH THE WRITTEN DESCRIPTION REQUIREMENT UNDER 35 U.S.C. § 112, FIRST PARAGAPH WITH RESPECT TO AN IMMUNOMODULATING DRUG

The Examiner has rejected claim 22 as lacking sufficient written description. Claim 22 is directed to a method of treating systemic lupus erythematosus in a human patient comprising administering to the patient an effective dose of a CD1d blocking antibody and a second therapeutic agent for treatment of systemic lupus erythematosus, wherein the second therapeutic agent is a non-steroidal anti-inflammatory drug, corticosteroid, immunomodulating drug and/or an anticoagulant.

Claim 22 complies with 35 U.S.C. § 112, first paragraph, because the specification provides sufficient written description with respect to an immunomodulating drug. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art

that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966).

Furthermore, what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94; *See also*, *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005)("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge.... As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution."). If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

In the instant case, the Examiner appears to take issue with the claim element "immuno-modulating drug". In particular, the Examiner asserts that "[t]he species of immunomodulating drugs disclosed in the instant specification have different structures and mechanisms of action. The specification does not disclose a structure/function relationship for immmunomodulating drugs that modulate some aspect of an immune response that alleviate symptoms of lupus and work in tandem with CD1d-blocking antibody." (Office Action, page 3, paragraph 4). The Examiner further asserts that the specification does not disclose any other drugs besides the "six drugs that are immuno-modulating drugs" (i.e., methotrexate, cyclosporine, chloroquine, hydroxycloroquine, azathioprine and cyclophosphamide). OA, p. 3, last paragraph.

It is respectfully pointed out that the Examiner's concern with structure to function relationship is misplaced and incorrect. First, the structure to function correlation of an immunomodulatory agent is sufficiently disclosed. Second, one of ordinary skill in the art would understand the plain meaning of immunomodulatory agent in terms of treating lupus. Third, the

specification provides additional examples beyond the purported six on which the Examiner focuses. Fourth, one of skill would recognize what are immunomodulating agents based on conventional knowledge in the relevant art.

Indeed with respect to the foregoing points, the specification explicitly teaches (page 2, paragraph 0006):

> A variety of biologic agents are under investigation as potential treatments for SLE. These products are designed to specifically interfere with immunologic processes, including T cell activation; T cell-B cell collaboration; production of antidouble-stranded DNA antibodies; deposition of anti-double-stranded DNA antibody complexes; complement activation, and immune complex deposition and cytokine activation and modulation. More aggressive interventions include gene therapy and stem cell transplantation. **Immunomodulatory agents recently tested include thalidomide, ASlO1,2' chlordeoxyadenosine, mycophenolate mofetil, and bindarit**. Additional pharmaceutical treatments include the mild androgen dehydroepiandrosterone, selective estrogen receptor modulators, and the prolactin inhibitor, bromocriptine. (emphasis added)

The specification, at least as illustrated by the foregoing disclosure, provides various aspects of the immune reaction that can be modulated by immunomodulatory agents, including T cell activation, T cell-B cell collaboration or complement activation to name a few. One of skill would recognize and readily be able to identify immunomodulatory agents that function in the preceding manner. Furthermore, upon reading the entirety of the instant specification, one of ordinary skill in the art would comprehend that "immunomodulatory agents" are in the context of treating lupus. In addition, as the exemplary disclosure above makes clear, the Examiner has overlooked and clearly missed entire portions of the specification which disclose and characterize immunomodulatory agents (i.e., more than the six the Examiner purports). Moreover, the Examiner has clearly failed to appreciate immunomodulatory agents which are known and conventional in the relevant art (e.g., thalidomide, ASlO1,2' chlordeoxyadenosine, mycophenolate mofetil, and bindarit). Furthermore, with a basic understanding of immunomodulatory agents known in the art, and upon reading the instant disclosure, one or

ordinary skill in the art would immediately appreciate the claimed method of treating lupus with the CD1d blocking antibody and immunomodulatory agent.

In sum, claim 22 is sufficiently described in the instant specification. The Examiner has erred in the rejection and it is respectfully requested that the rejection be reversed.

B. THE EXAMINER ERRED IN REJECTING CLAIMS 15-26 AS UNPATENTABLE UNDER 35 U.S.C. § 103(a)

The Examiner has rejected claims 15-26 as being obvious over a combination of five to seven references applied in four separate rejections under 35 U.S.C. § 103(a), each of which is addressed in turn below.

In order to establish a prima facie case of obviousness, the Examiner must demonstrate that the prior art (i) teaches or suggests every claim limitation, (ii) provides a motivation to combine (or modify) the teachings of the selected references, and (iii) provides a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488,20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143. Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness". *KSR Int '1 Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)). Thus, in order to establish a prima facie case of obviousness, it is necessary for the Examiner to identify the reasons why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. Moreover, it is improper for the Examiner to use the claimed invention as a blueprint for abstracting individual teachings from the cited references, as this is not a proper basis for an art-based rejection. *Ashland Oil Inc. v. Delta Resins & Refractories Inc.*, 776 F2d 281, 297 (Fed. Cir. 1985).

The Examiner has abstracted together individual teachings from the cited references, which simply cannot be combined to arrive at the claimed subject matter. Applicants respectfully submit that there is no motivation to combine the teachings cited by the Examiner in a manner that results in Applicant's claimed invention.

1. Claims 15-20 and 23-26 are patentable under 35 U.S.C. 103(a) over Amano, in view of Kotzin, Zeng, Blumberg and Hughes.

The Applicants' claims are directed to a method of treating lupus in a human patient by administering CD1d blocking antibody. In the Office Action mailed February 06, 2008 (hereinafter "Office Action"), the Examiner provides a combination of various disclosures of the cited references Amano, Kotzin, Zeng, Blumberg and Hughes, but without any real cogent basis as to why one of skill would be led to combine the various individual teachings to arrive at the claimed process.

a) Summary of Cited Art

The primary reference, Amano, discusses T cells that carry the $V_\beta 9$, $V_\alpha 4.4$ T cell receptor (TCR). More particularly, Amano discloses that CD1 expression defines subsets of follicular and marginal zone B cells in the spleen and that such B cells may be a critical site for interactions between T and B cells for certain subsets of microbial antigens. The reference does not teach or suggest treatment of lupus as in the claimed subject matter. A more complete discussion of this and additional references can be found in the following explanations of why the claimed inventions would not have been obvious from the combined prior art.

i. *Amano does not render the claimed invention obvious*

The Examiner asserts in salient part the following: (1) Amano allegedly teaches that the interaction between anti-CD1 T cells and B cells leads to mutual activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity via CD1 cross-linking resulting in secretion of IgM and IgG. (Office Action, page 4, last paragraph); (2) Amano allegedly teaches that T cell proliferation of a CD1-restricted T cell clone in response to CD1-transfected B cells could be blocked by use of an anti-CD1d monoclonal antibody ("mAb"). *Id.*; and (3) Amano allegedly teaches that CD1 appears to be recognized by a T cell subset which has a restricted TCR repertoire that is made up predominantly of an invariant rearrangement of the $V_\alpha 14J_\alpha 281$ associated with $V_\beta 2$, $V_\beta 7$, $V_\beta 8$ receptors, and that T cells that do not express NK1.1 marker or $V_\alpha 14$ TCR are able to recognize CD1 on syngenic antigen presenting cells. The Examiner also asserts that Amano does "not teach the claimed method of treating pathogenic polyclonal B cell activation or class switching, including that resulting in lupus (SLE), in a human patient, comprising administering a CD1 [CD1d] blocking agent that is an antibody, including a monoclonal antibody." Office Action, p. 5.

The Examiner essentially provides a listing of various alleged disclosures by Amano without any conclusion or rationale as to how such assertions, even if correct, would render the claimed invention unpatentable. Indeed, the teachings whether alone or combined with the other cited art cannot lead to the claimed invention, because Amano do not provide a reasonable expectation of success or an adequate level of predictability to administer anti-CD1d antibody to treat lupus.

The Amano reference provides an *in vitro* experimental model which is an absolutely artificial system that uses one T cell line that is genetically engineered to express a receptor that recognizes CD1. Put another way, 100% of the cells have a receptor that they would not normally have and which does not occur in a native *in vivo* system (e.g., subject or patient). Furthermore, Amano demonstrate that this T cell line proliferates in response to exposure to the CD1d expressed on the surface of B cells. In contrast, with lupus, it is the proliferation of B cells and the secretion of antibodies coupled with the later switching of antibody class that form the hallmarks of the disease. None of these phenomena are demonstrated or even suggested by the Amano reference. The demonstration of inhibition of T cell proliferation with an anti-CD1d antibody in Amano of does not teach or suggest the use of this antibody to treat lupus since there is no demonstration or suggestion that NKT cells, let alone T cells, can stimulate the proliferation of B cells. With no demonstration or suggestion that this interaction occurs, there can be no suggestion that it is beneficial to block the interaction to prevent B cell proliferation.

Additionally, at the time of invention, it was known that deletion of $CD4^+$ T cells, a much larger cell population then NKT cells, effectively treats disease. Knowing this fact, a person of skill would not be led to believe that lupus could be treated by targeting a small cell population like the 3-4% in mice or the 0.1% in humans that NKT cells represent out of the total T cell population. Instead, a person of skill would retain the commonly held believe that another, larger cell population was involved in the etiology of lupus and would not look upon the results of Amano with any expectation of success, particularly since Amano does not demonstrate that NKT cells or even T cells stimulate B cells to proliferate, secrete antibodies and to later undergo class switching.

The alleged interaction between anti-CD1 T cells and B cells that leads to mutual activation of both cell types with resultant hypergammaglobulinemia and systemic autoimmunity is attributed by Amano to Zeng and will be addressed in section 1.a.ii. below.

Moreover, even assuming *arguendo* that Amano when combined with Zeng suggest that CD1d is implicated in SLE, this would not rise to the level of suggesting that blocking CD1d would be effective in treating the disease.

ii. *Zeng in view of Amano does not render the claimed invention obvious*

As with Amano, the secondary reference Zeng also discusses an artificial system, this time consisting of a transgenic mouse model where all the T cells carry the $V_\beta 9$, $V_\alpha 4.4$ T cell receptor (TCR). Furthermore, Zeng teaches that subsets of transplanted transgenic T cells that recognize CD1 may either **induce** or **prevent** murine lupus in recipient mice, thus explicitly outlining the unpredictability associated with T cell involvement. Zeng also discloses using anti-CD1d antibody for isolation of an IgM fraction from anti-CD1 hybridoma supernatants.

Further unpredictability of the references is demonstrate by the fact that when the $V_\beta 9$, $V_\alpha 4.4$ receptor from Amano is expressed as a transgene in Zeng, two types of T cells were created. One transgenic mouse had T cells with single positive cells (CD4+CD8- or CD4-CD8+), while a second transgenic mouse had double negative cells (CD4-CD8-) like those in Amano. Zeng found that the injection of the double negative cells were protective of disease, while the single positive cells, which do not correspond to the original cell type, caused a disease phenotype. A person of skill in the art when presented with this data would be confused as to the relevance of the interaction between T cells and B cells since these are two examples of T cells with the same receptor producing contradictory results in the same model.

In contrast, Applicant used a non-genetically engineered, hereditary model of lupus where NKT cells are present at about 3-4% of CD4+ T cell populations. Applicant further demonstrated that these CD1 reactive cells (NKT cells) are involved in mediating lupus and that blocking CD1d ameliorates disease. Furthermore, in contrast to the artificial model provided in Amano and Zeng, Applicant shows that by administering anti-CD1d antibody, onset of disease (e.g., proteinuria) is delayed and survival is prolonged. Without an understanding that NKT cells mediate disease, one would simply not apprehend the disclosure of Amano and Zeng (below) to suggest with any reasonable predictability the treatment of lupus by administration of anti-CD1d antibody. Furthermore, in the transgenic mice, the receptor for CD1d is found on all the T cells, while conversely it is only present on about 0.1% of the greater T cell population (i.e., NKT cells) in

humans. As such, at the time of invention, one would not reasonably extrapolate from the results seen with the universal expression of the CD1d receptor in Amano and Zeng, to the treatment of humans with an anti-CD1d antibody with any expectation of success given the exceedingly small prevalence of NKT cells in humans.

iii. *Kotzin alone or in combination with any of the cited prior art does not render the claimed invention obvious*

The tertiary reference Kotzin is a review article which discusses production of IgG autoantibody production in SLE. The Examiner asserts that Kotzin allegedly teaches IgG autoantibody production in SLE by clonal expansion of somatically mutated anti-DNA antibody-producing B cells. Office Action, p. 5. Furthermore, the Examiner asserts that Kotzin teaches that IgG antibodies to ds-DNA appear to play a role in immune complex glomerulonephritis of SLE. In sum, it is unclear what the Examiner's reasoning is in citing Kotzin and how or for what reason one of skill at the time of invention would view Kotzin as suggestive to administer any antibody, save anti-CD1d, to treat lupus. Here, as with Amano and Zeng, the Examiner merely recites every purported disclosure of the cited reference without establishing any nexus between the teachings or articulating a reasonable basis for arriving at the claimed invention.

The additional references Blumberg and Hughes, respectively, discuss cell selection/identification using various CD1 antibodies and the concept of humanizing monoclonal antibodies generally, and therefore, do not provide a rationale for using the anti-CD1d antibodies in treatment of lupus. The references do not cure the deficiencies of the other references used in the rejection.

b) Examiner's Rationale

The Examiner's conclusion is recited as follows (OA, page 7):

> It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the anti-CD1d mAB taught by Zeng *et al* or Amano *et al* the anti-CD1d antibodies taught by Blumberg *et al* to block CD1 recognition by T cells as taught by Amano *et al* by administration of antibodies to human patients with SLE, and hence to treat pathogenic polyclonal B cell activation or class switching taught by Kotzin *et al*, including with humanized versions of the said antibodies as taught by Hughes for human patients with autoimmune diseases, and including by the intravenous (IV) route of administration of T cells by

> Zeng *et al.* One of ordinary skill in the art at the time the invention was made would have been motivated to do this to treat pathogenic polyclonal B cell activation or class switching in a patient with SLE with a reasonable certainty of success because...[OA, pages 7-8 omitted].

In reviewing the foregoing recitation, as well as the omitted sections provided in two full pages (OA, pages 7-8), there is no reasoned basis or sufficient rationale provided as to why the recited disclosures should be combined, and even if combined how one of skill would arrive at the claimed invention. It is apparent that the Examiner is improperly abstracting individual teachings of the cited references based on the Applicant's invention. In the explanation of what the references teach and what would have been obvious, the Examiner provides an inventory of virtually every disclosure in the cited references. OA, pages 4-7. This extensive listing actually reinforces the non-obviousness of the claimed inventions. As to the claimed methods, it appears the Examiner is primarily relying on the Amano, Zeng and Kotzin references; a summary of the alleged teachings of these references is provided above.

The Examiner asserts that Amano does not teach treating pathogenic polyclonal B cell activation or class switching, through administration of a CD1 blocking antibody. OA, page 5, second full paragraph. The Examiner also asserts that Kotzin discloses clonal expansion of B cells producing IgG autoantibody, which mimics normal T cell dependent response to foreign antigen, involving common mechanisms of affinity maturation and IgM to IgG class switching. OA, page 5, third paragraph. The Examiner appears to be alleging that because Amano and Zeng allegedly disclose T cell-B cell interaction through CD1, and Kotzin allegedly discloses involvement of B cell class switching in lupus, then it would have been obvious to treat lupus by administering anti-CD1d antibody to a human subject. However, such construction is necessarily built on improper hindsight reasoning, because at the time of invention the prior art held the misconstrued view that $CD4^+$ helper T cell involvement induced B cell activation (or proliferation) or class switching. (*infra*, Swain, SL, 1983; Swain et al. 1984; Wofsy and Seaman, 1985). Moreover, none of the references actually show any treatment of lupus and one would not have ay expectation of success from the combined teachings of the references.

As further explained in the discussion below, the combination of references is both improper and would not have led one of ordinary skill in the art at the time of invention to consider CD1d antibody therapy for lupus.

c) Combination of Cited References Does Not Lead to Claimed Invention

The claimed subject matter is not rendered obvious by the cited prior art because at the time of the invention, the collective view held that it was the interaction of $CD4^+$ helper T cells with B cells that induced B cells to proliferate, secrete autoantibodies and undergo class switching from IgM to IgG. See Swain SL. Immunol. Rev. 74:129, 1983; and Swain et al. J. Immunol. 132:1118-23, 1984. This teaching away was reinforced by the demonstration that depletion of $CD4^+$ helper T cells with anti-CD4 mAb ameliorated lupus in the hereditary murine model NZB/NZW F1. See Wofsy D, and Seaman SE. J. Exp. Med., 161:378-91, 1985.

In other words, CD1d and NKT cells as disclosed in the instant specification were not believed to be involved in the etiology of lupus. Thus, the prior art taught away from Applicant's discovery that CD1d and NKT cells are important effectors in the etiology of lupus.

The claims are directed to a method of treating a human patient by administering a CD1d blocking antibody, which inhibits pathological polyclonal B cell activation or class switching (e.g., claim 16). The fact of the matter is that none of the cited references show or suggest treating lupus by administering CD1 blocking antibody. The Examiner misapprehends either what is encompassed by the instant claims or what Amano – the primary reference – teaches. For example, the Examiner states (emphasis added):

> Applicant argues that Zeng does not teach the role of NK T cells in lupus because the experiments (Amano and Zeng) did not study NK T cells, the arguments based on upon the assertion that the transgenic mouse model used carried the Vα4.4 TCR, but that NK T cells express Vα14 TCR. Applicant further argues that it would not have been predictable that spontaneous lupus found in NZB/NZW mice that express Vα14 TCR (Applicant's model) could be treated with an anti-CD1d antibody. **However, Amano *et al* teach that the Vα4.4 T cell clone proliferates in response to CD1-transfected B cells, that this proliferation is blocked by an anti-CD1d mAb, and that this T cell clone can induce lupus.**

More particularly, as underscored by the highlighted portion above, and acknowledged by the Examiner, Amano did not demonstrate that a T cell clone could induce the proliferation of B cells, B cell activation with the resultant secretion of antibodies or class switching of antibody type from IgM to IgG. See page 1714, 2nd column, 1st paragraph under heading *T cell recognition of CD1 is not associated with* $\beta_2 m$. Instead, Amano demonstrated the opposite result by showing that a transgenically derived T cell clone, Vβ9/Vα4.4, vigorously proliferated in response to a CD1-transfected B cell line.

In addition, there is no reason to generalize that one CD1d recognizing T cell clone that induces lupus shows or implies that all CD1d recognizing T cells will induce lupus. In fact, Zeng teaches that CD1d recognizing transgenic T cells can induce or suppress lupus depending on the tissue of origin and the cytokine secretion pattern. Furthermore, the finding that one CD1d recognizing T cell clone can induce lupus does not teach whether the considerably more numerous MHC recognizing CD4+ T cells will induce lupus also. Lupus induction by these MHC recognizing T cells would not be expected to be blocked by anti-CD1d monoclonal antibody. Therefore, Zeng does not teach that all CD1d recognizing T cells induce lupus or that MHC recognizing T cells do not induce lupus or that any T cell that induces lupus can be blocked with an anti-CD1d monoclonal antibody or that spontaneously occurring lupus can be blocked with an anti-CD1d monoclonal antibody. There was no reason to expect at the time of the paper of Zeng that the cellular and molecular mechanisms that cause lupus induced by CD1d recognizing transgenic T cells derived from a single T cell clone are the same or similar to the mechanisms that cause spontaneous lupus in mice or humans.

A key finding by the Applicant, which provides the reasoning to treat lupus with antibodies against CD1d, is that NKT cells mediate B cell activation and class switching, thus resulting in lupus. Both Amano and Zeng are limited to the convention in the prior art that conventional T cells are involved in the etiology of lupus. Declaration of Dr. Samuel Strober, paragraphs 4-5 (hereinafter "Declaration"). In contrast, Applicant discovered that it is the NKT cell mediation of antibody production and isotype switching that results in disease. For example, as discovered by Applicant, incubation of conventional T cells with B cells does not result in significantly increased secretion of IgM or IgG isotypes as compared to cultures of B cells alone. Declaration, paragraph 5.

However, co-culturing NKT cells with splenic B-1 or marginal zone B cells secreted markedly increased amounts of IgM and IgM anti-dsDNA antibodies. *Id.*

Amano does not teach about the interaction of CD1 and NKT cells because the cell line used for the experiments was a T cell line that was engineered to express the $V_\beta 9$, $V_\alpha 4.4$ TCR. In contrast, the NKT cells from NZB/W mice, as described in the instant specification, express $V_\alpha 14J_\alpha 18$. The use of an engineered cell line that does not have the correct TCR is further evidence that the model of Amano and Zeng would not be predictive of success in administering anti-CD1d antibodies in treatment of SLE in humans.

Zeng does not teach the role of NKT cells in lupus, because the experiments did not study NKT cells. Instead, a transgenic mouse model was used where all of the T cells carried the $V_\beta 9$, $V_\alpha 4.4$ TCR. NKT cells, on the other hand, express a unique and invariant TCR, $V_\alpha 14J_\alpha 18$. Furthermore, the Zeng's teachings were limited to *in vitro* demonstrations that transgenically derived T cells expressing the CD1d TCR transgenes could stimulate the proliferation of non-transgenic B cells. However, importantly, in the transgenic animal model these T cells did not cause the development of lupus. See Zeng, page 527, column 1, first paragraph. Thus, contrary to the Examiner's assertion, there would not be an expectation of success in the claimed method of treatment, particularly since in humans only 0.1% of the T cells are NKT cells as opposed to 100% of the cells in the Zeng model. Furthermore, at the time of invention, NKT cells were believed to be protective and not causative for lupus.

Only when Zeng. transferred T cells from transgenic mice to irradiated *nu/nu* host mice were they able to induce lupus. Even here, only certain subsets of T cells induced disease notwithstanding the fact that 100% of the T cells expressed the CD1d TCR transgenes. Normally, in mice, the CD1d TCR is only found on NKT cells which make up approximately 3-4% of the greater T cell family.

More specifically, Zeng transplanted bone marrow with or without added sorted T cells. T cells were sorted based on CD4 and CD8 expression and were also classified as to organ source. When bone marrow from single positive (SP, i.e., $CD4^+$ or $CD8^+$) transgenic mice was injected into irradiated hosts, 9 of 20 developed ascites, and 15 of 20 developed proteinuria and anti-double stranded DNA antibodies; the three markers for lupus. See page 527, column 2, last paragraph and Table 2. Bone marrow from double negative (DN, i.e., $CD4^-$ and $CD8^-$) transgenic mice did not

induce disease in 12 of 12 host mice. See page 528, column 1, lines 8-11 and Table 2. SP bone marrow admixed with splenic SP sorted T cells induced disease in 6 of 6 mice. See page 528, column 1, lines 3-8 and Table 2. The addition of splenic DN sorted T cells accelerated disease induction when admixed with SP bone marrow. See page 529, column 1, lines 20 – column 2, lines 1-2. Bone marrow from nontransgenic nude mice admixed with splenic SP T cells induced two of the three hallmarks of lupus, as did non-transgenic nude mouse bone marrow admixed with splenic DN T cells. See page 529, column 1, second paragraph and Table 2. Bone marrow from nontransgenic nude mice admixed with $CD4^+$ or $CD8^+$ sorted T cells induced two of the three hallmarks of lupus. See Table 2.

Mixing experiments of bone marrow cells suggested bone marrow from DN mice may reduce the incidence of disease when added to SP bone marrow as 2 of 8 mice developed all three hallmarks of lupus compared to 9 or 15 of 20 mice developing the individual hallmarks of lupus in mice that received only SP bone marrow. See page 529, column 2, section entitled $CD4^-CD8^-$ T Cells from Transgenic Marrow Prevent Lupus and Table 3. Further experiments demonstrated the importance of the organ source of DN T cells with bone marrow derived DN T cells suppressive and splenic DN T cells causative of disease. See Table 3. Zeng concluded that "[t]he inhibitory activity of the DN transgenic BM cells was related to the presence of the transgenes, since substituting 2.5 x 10^6 BM cells from nontransgenic BALB/C mice failed to inhibit the induction of lupus abnomalities by the SP transgenic BM cells." See page 529, column 2, lines 25-30.

Unable to correlate the induction of disease with CD4 or CD8 status, Zeng next studied the cytokine expression pattern of the transgenic T cells and discovered that bone marrow DN T cells had the Th2 secretion pattern with high levels of IL-4 and relatively low levels of IFN-γ and IL-2. In contrast, SP, double positive ($CD4^+$ and $CD8^+$), and splenic DN T cells exhibited the Th1 cytokine expression pattern with high levels of IFN-γ and IL-2 and relatively low levels of IL-4. See page 529, column 2, section entitled: Cytokine Profile of Transgenic T Cells That Induce or Prevent Lupus.

In sum, at the time of invention there would be no reasonable expectation of success, for one of skill to treat lupus using anti-CD1d antibody, because one of skill would have recognized at the time of invention that Amano and Zeng provide an artificial system that does not reflect what

actually occurs (i.e., Applicants' discovery of the unexpected result where NKT cells activate CD1 on B cells sufficiently for the development of a pathology) and is not a representative system from which a person of art could reasonably extrapolate to the treatment of humans.

Moreover, one of ordinary skill in the art at the time of invention needed to consider the entire teachings of the cited references as a whole and not extract isolated portions. As such, the preponderance of the teachings of the Amano and Zeng would be more confounding than predictive and would not have led to the instantly claimed methods.

In particular, one of skill would not have been motivated to combine the aspects from the studies presented by Amano and Zeng together or with the other cited references because it would be known that 1) normal mice only express CD1d TCR on NKT cells and not on T cells, 2) NKT cells only represent 3-4% of the greater T cell population in mice and 0.1% in humans, 3) the T cells used for the experiments were isolated from transgenic mice where 100% of the T cells express CD1d TCR, 4) the transgenic mice do not develop disease, 5) the recipient mice were lethally irradiated to condition them for accepting the donor cells, 6) disease was only induced in some recipient mice, 7) no correlation was found for T cell markers and disease induction, and 8) Zeng specifically concluded that the presence of the transgenes in bone marrow T cells is inhibitory for the development of lupus. Therefore, one of skill would not be led to conclude that the combination of the results of Amano and Zeng are applicable to arriving at the claimed inventions, because Amano and Zeng do not teach or suggest that administration of anti-CD1d antibody could treat lupus.

Rather than finding motivation to combine references, the person of ordinary skill in the art would espouse the conventional view that $CD4^+$ helper T cells are required for activation of B cells because $CD4^+$ helper T cells are more prevalent than NKT cells and it was known that the deletion of $CD4^+$ helper T cells by anti-CD4 antibodies would ameliorate disease in hereditary murine models in a simple and direct manner.

Moreover, even if one CD1d recognizing T cell clone could induce lupus there is nothing in Amano or Zeng to show or imply that all CD1d recognizing T cells will induce lupus, not withstanding the fact that in Zeng transgenic T cells with the same receptor can induce or suppress lupus depending on the tissue of origin and the cytokine secretion pattern. Furthermore, the finding that one CD1d recognizing T cell clone can induce lupus does not teach whether the considerably

more numerous MHC recognizing CD4+ T cells will induce lupus also. Lupus induction by these MHC recognizing T cells would not be expected to be blocked by anti-CD1d monoclonal antibody. Therefore, Zeng does not teach that all CD1d recognizing T cells induce lupus or that MHC recognizing T cells do not induce lupus or that any T cell that induces lupus can be blocked with an anti-CD1d monoclonal antibody or that spontaneously occurring lupus can be blocked with an anti-CD1d monoclonal antibody. There was no reason to expect at the time of the paper of Zeng that the cellular and molecular mechanisms that cause lupus induced by CD1d recognizing transgenic T cells derived from a single T cell clone are the same or similar to the mechanisms that cause spontaneous lupus in mice or humans.

Applicants now have clinical data to further support the discovery that blocking CD1d TCRs with antibody reduces the secretion of anti-double stranded DNA antibodies, a marker for lupus. *See, e.g.*, Declaration, paragraph 5. Normal CD-19$^+$ B cells do not spontaneously secrete IgM or IgA in culture. When normal NKT cells are added, IgM and IgA secretion is detected. In contrast, CD-19$^+$ B cells from lupus patient spontaneously secrete considerable amounts of IgM, IgA and IgG. When co-cultured with NKT cells, B cells increased antibody production 2-10 fold. When anti-CD1d antibody was added anti-double stranded DNA IgG production was significantly reduced.

In sum, the Examiner erred in the rejection of the instant claims. The Examiner has failed to establish a prima facie case of obviousness, because the Examiner has failed to establish a reasonable basis for combining the multiple cited references and the Examiner has failed to establish a reasonable expectation of success based on knowledge in the relevant art at the time of invention.

For the reasons described above, claims 15-20 and 23-26 are not obvious under 35 U.S.C. § 103 and are therefore patentable. Therefore, the Examiner has erred in the rejection and the Examiner's obviousness rejection should be reversed.

2. Claims 21 and 22 are patentable under 35 U.S.C. 103(a) over Amano, in view of Kotzin, Zeng, Blumberg, Hughes and Merck Manual.

Claim 21 is dependent from claim 15 and is directed to a method of treating a human subject for lupus erythematosus by administering a second therapeutic agent for treating SLE. Claim 22 further defines options for such second therapeutic agents.

For the reasons provided above (Section VII(B)(1)), the combined teachings of the cited references do not teach or suggest the claimed subject matter of independent claim 15. The Merck Manual does not cure the deficiencies in the grounds of rejection as presented. As such, dependent claims which require claim elements of intervening claims are also necessarily patentable.

Therefore, the Examiner's obviousness rejection should be reversed.

3. Claims 15-26 are patentable under 35 U.S.C. 103(a) over Amano, in view of Kotzin, Zeng, Blumberg, the '453 patent, Hughes and Merck Manual.

The Examiner submits a rejection for claims 15-26 based on the above captioned references and a separate rejection based on the above captioned references and the Merck Manual reference (i.e., 6 and 7 references respectively). In the interest of obviating redundancy, both rejections are addressed here.

The Examiner repeats the purported teachings of Amano and Zeng consonant with what is discussed above. In addition, the Examiner asserts that the '453 patent discloses that a decrease in Vα14 NK T cells is closely associated with the onset of lupus in a murine model. OA, page 14, paragraph 2. This association contradicts the Examiner's previous assertions regarding the significance of Amano as presented in the Office Action at page 12, bottom paragraph. For if T cell proliferation can be blocked by the use of an anti-CD1d antibody a person of skill would reasonably conclude that the use of an anti-CD1d antibody would be contraindicated in the treatment of lupus because, administration of the antibody would be expected to further depress NKT cell number by blocking their proliferation and thereby accelerate the development of the disease.

In sum, the Examiner has failed to establish a prima facie case of obviousness as set forth above, and the addition of the disclosure of the '453 patent to the purported teaching of Amano and Zeng does not provide a reasonable basis for combining these multiple cited references.

Furthermore, the Examiner has failed to establish a reasonable expectation of success based on knowledge in the relevant art at the time of invention.

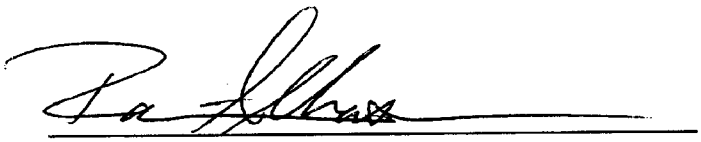
For the reasons described above, claims 15-26 are not obvious under 35 U.S.C. § 103 and are therefore patentable. Therefore, the Examiner has erred in the rejection and Examiner's obviousness rejection should be reversed.

CONCLUSION

For the reasons stated above, claims 15-26 are patentable over the prior art of record, and the rejection of claim 22 under 35 U.S.C. § 112, written description, is improper. Appellants respectfully request the Board to reverse the Examiner's rejections with instructions to allow the claims.

The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account No. 23-2415 (Attorney Docket No. 31580-702.201).

Respectfully submitted,

Date: December 1, 2008 By: 

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VIII. CLAIMS APPENDIX

1-14. (Canceled)

15. (Previously Presented) A method of treating systemic lupus erythematosus in a human patient comprising administering to said patient an effective dose of a CD1d blocking antibody, wherein said effective dose treats said systemic lupus erythematosus in said human patient.

16. (Previously Presented) The method of Claim 15 wherein said administration inhibits a pathologic polyclonal B cell activation or class switching.

17. (Previously Presented) The method according to Claim 15, wherein said antibody is a monoclonal antibody.

18. (Previously Presented) The method according to Claim 17, wherein said monoclonal antibody is a human or humanized antibody.

19. (Previously Presented) The method according to Claim 17, wherein said monoclonal antibody specifically binds to human CD1d.

20. (Previously Presented) The method according to Claim 15, wherein said administration is by intravenous injection.

21. (Previously Presented) A method according to Claim 15, further comprising administering to said patient a second therapeutic agent for the treatment of systemic lupus erythematosus.

22. (Previously Presented) The method of Claim 21, wherein said second therapeutic agent is a non-steroidal anti-inflammatory drug, corticosteroid, immunomodulating drug, and/or an anticoagulant.

23. (Previously Presented) A method of treating systemic lupus erythematosus in a human patient comprising administering to said patient an effective dose of a CD1d blocking antibody, wherein said effective dose treats said systemic lupus erythematosus in said human patient and inhibits a pathologic polyclonal B cell activation or class switching.

24. (Previously Presented) A method of treating systemic lupus erythematosus in a human patient comprising administering to said patient an effective dose of a CD1d blocking antibody, wherein said effective dose treats said systemic lupus erythematosus in said human patient and delays the onset of proteinuria.

25. (Previously Presented) The method according to Claim 24, wherein said administering to said patient an effective dose of a CD1d blocking antibody reduces the levels of serum IgG and anti-dsDNA IgG.

26. (Previously Presented) The method according to Claim 24, wherein said administering to said patient an effective dose of a CD1d blocking antibody prolongs survival of said patient.

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.